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Systematic review and meta-analysis protocol examining the effect of vitamin D status and supplementation on urinary tract infection V.2

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ABSTRACT

Several studies have demonstrated that vitamin D deficiency was associated with an increased incidence of infectious disease, including urinary tract diseases. The present systematic review aims to investigate whether vitamin D deficiency is associated with an increased incidence of urinary tract infections (UTI) and whether supplementation could reduce the risk of UTI. This systematic review and meta-analysis will be carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The search will be performed using multiple databases, including MEDLINE, CENTRAL, ClinicalTrials.gov. We will screen observational studies and interventional studies with our inclusion criteria and assessed the quality with the Newcastle-Ottawa scale and Cochrane Risk of Bias tool. Currently we do not anticipate any problems with the implementation of the proposed protocol. The results of this study will explain the effects of vitamin D deficiency and the prevention role of vitamin D supplements on UTI.

Keywords: vitamin D, vitamin D deficiency, urinary tract infection

- 1 Review question: The present systematic review aims to investigate whether 25(OH)D levels differ among UTI patients and healthy participants, investigate the association between vitamin D status and UTI, and investigate the role of vitamin D supplementation to reduce UTI.

Population: General population without age, gender, and ethnicity restriction

Exposure: UTI patients, vitamin D deficiency patients, vitamin D supplementation group

Comparison: Non-UTI patients, participants with sufficient vitamin D status, control group Healthy pregnant women Outcome: Serum 25(OH)D level, OR of UTI

Study type: Systematic review and meta-analysis

- 2 Searches will be performed using multiple databases including MEDLINE, CENTRAL, ClinicalTrials.gov. The full reference list of the included studies will also be searched and managed using data management software. No date/language restrictions will be applied. The main search terms will include: "vitamin D deficiency, vitamin D, Vitamin D supplementation, urinary tract infection, cystitis, pyelonephritis " using their MeSH term.
- 3 Condition or domain being studied: Urinary tract infection (UTI) is one of the most common bacterial infections and has a high risk of recurrence. Several studies have demonstrated that vitamin D deficiency was found to be associated with UTI in children, women, and renal transplant. Vitamin D is known to play an important role in the first defense against bacterial infections; e.g. by induction of the antimicrobial proteins cathelicidin and β -defensin. There is increasing evidence that vitamin D deficiency plays an important role in susceptibility to infections. This present systematic review aim to investigate vitamin D status is associated with UTI and whether vitamin D supplementation could reduce the risk of UTI.
- 4 Participants/population: The study's population is general population in all age without gender and ethnicity restriction.
- 5 Intervention(s), exposure(s) : UTI patients, vitamin D deficiency patients, vitamin D supplementation group
- 6 Comparator(s)/control Control group: Non-UTI patients, participants with sufficient vitamin D status, control group

- 7** Types of study to be included: observational studies (prospective & retrospective cohorts, case-control, cross-sectional, nested case-control) as well as interventional studies (non-randomized control trial, randomized controlled trial, and crossover trial studies) will be included. Case-reports, small case series (<10 patients), letters to the editor, conference proceedings, animal studies and review articles will be excluded.
- 8** Main outcome(s) : Serum 25(OH)D level (ng/mL), OR of UTI
- 9** Data extraction: The process of study selection will be performed in 3 consecutive stages.
- Firstly, titles and abstracts of all electronic papers will be screened to assess their potential eligibility. All articles presumed to meet the criteria will be retrieved as full-texts. we screened abstract of retrieved article using mendeley reference manager software.
- Subsequently, all observational studies reporting the outcomes of interest will be selected. Data extraction will be made by two authors independently. Any possible discrepancies concerning retrieval of articles will be resolved through the consensus of all authors.
- The extracted data will include the following parameters: name of first author, year of publication, study design, number of participant, location of the study, participant's age, level of 25(OH)D, OR of UTI.
- 10** Risk of bias (quality) assessment The quality of the included studies will be evaluated using the Newcastle-Ottawa Scale (NOS) score. Case-control studies will be assessed regarding the risk of bias on the domains of patient selection, comparability of cases and controls, ascertainment of exposure and non-response rate. The risk of bias in cohort studies will be assessed on the basis of selection and comparability of the exposed and non-exposed cohorts, as well as the assessment of outcome and the adequacy of the follow-up period. For interventional study including RCT, we will use the Cochrane risk of bias assessment tools evaluating the following characteristics: random sequence generation, allocation concealment, selective reporting, participant and personnel. The NOS score and risk of bias will be evaluated by two authors independently; any disagreements will be resolved through their consensus.
- 11** Strategy for data synthesis: A qualitative synthesis is planned to performed as the expected inter-study heterogeneity is high due to differentiations of population across different settings. The odds ratio (OR) and its 95% confidence interval (95% CI) will be used for binary outcomes, and the mean difference (MD) and its 95% CI for the continuous outcomes. If $p < 0.05$, we will consider the difference to have statistical significance. I² test will be applied to test heterogeneity of the included studies. If the included studies have no or small heterogeneity ($p > 0.1$, $I^2 < 50\%$) the fixed-effect model will be used to synthesize data. If the heterogeneity is obvious ($p < 0.1$, $I^2 > 50\%$), we will choose random-effect derSimoian model.

- 12** Analysis of subgroups or subsets Subgroup analysis will be performed explore heterogeneity based on study age group, gender, location of the study, design of the study, cut-off definition of vitamin D deficiency.